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ORIGINAL COMMUNICATION

Prevalences of hyperhomocysteinemia, unfavorable cholesterol profile and hypertension in European populations

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Background: Hyperhomocysteinemia (HHCY) is a risk factor for cardiovascular diseases (CVD). HHCY may interact with hypertension (HTEN) and an unfavorable cholesterol profile (UNFAVCHOL) to alter the risk of CVD.
Objectives: To estimate the prevalences of HHCY (1) isolated and (2) in combination with UNFAVCHOL and/or HTEN in different age categories. To provide information that may improve the screening and treatment of subjects at risk of CVD.
Design: Cross-sectional data on 12 541 men and 12 948 women aged 20 + y were used from nine European studies.
Results: The prevalence of isolated HHCY was 8.5% in subjects aged 20–40 y, 4.7% in subjects aged 40–60 y and 5.9% in subjects aged over 60 y. When combining all age groups, 5.3% had isolated HHCY and an additional 5.6% had HHCY in combination with HTEN and/or UNFAVCHOL. The combinations of risk factors increased with age and, except for HHCY&UNFAVCHOL, were more prevalent than predicted by chance. Of the young subjects (20–40 y), 24% suffered from one or more of the investigated CVD risk factors. This figure was 75.1% in the old subjects (60 + years).
Conclusions: A substantial number of subjects in selected European populations have HHCY (10.9%). In half of these cases, subjects suffer also from other CVD risk factors like UNFAVCHOL and HTEN. Older people in particular tend to have more than one risk factor. Healthcare professionals should be aware of this when screening and treating older people not only for the conventional CVD risk factors like UNFAVCHOL and HTEN but also HHCY, as this can easily be reduced through increased intake of folic acid via supplement or foods fortified with folic acid.
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Introduction

Meta-analyses consistently report that elevated plasma total homocysteine (tHcy) concentrations increase the risk of cardiovascular disease (CVD) (The Homocysteine Studies Collaboration, 2002; Klerk *et al*, 2002; Wald *et al*, 2002). A 25% reduction in tHcy concentration (about 3 μmol/l) is estimated to result in an 11% lower risk of ischemic heart

disease and in a 19% lower risk of stroke (The Homocysteine Studies Collaboration, 2002). Hyperhomocysteinemia (HHCY) is of particular concern in subjects with other risk factors (de Bree *et al*, 2002), like those with hypertension (HTEN) (Vollset *et al*, 2001) or with an unfavorable cholesterol profile (UNFAVCHOL) (Graham *et al*, 1997).

Plasma tHcy concentration correlates weakly with blood pressure and cholesterol concentration, but in the direction of an increased risk of CVD, for example, the tHcy concentration is positively associated with systolic blood pressure and negatively with the HDL cholesterol concentration (Alfthan *et al*, 1994; Brattstrom *et al*, 1994; Arnesen *et al*, 1995; Nygard *et al*, 1995; Malinow *et al*, 1996; de Bree *et al*, 2001a). Suffering from more than one of these risk factors can have an additive or multiplicative effect on the risk of CVD. The latter finding was reported in the European Concerted Action Project (Graham *et al*, 1997).

Information on the prevalence of HHCY in isolation or in combination with HTEN and/or UNFAVCHOL in European populations is not available. To obtain such information, a random sample of the source population is needed. For practical and financial reasons, this was not possible for the present study. In order to obtain an reasonable estimate of these prevalences, available data were combined from published and unpublished studies. The data presented in this paper should therefore be seen as an initial estimate of the prevalences of HHCY, HTEN and UNFAVCHOL in a nonrandom sample of several European populations. Despite these limitations, this study gives an important first indication of the percentage of young, middle-aged and elderly subjects who are at increased risk of CVD due to HHCY, either isolated or in combination with UNFAVCHOL and/or HYPTEN. Such information is important for healthcare profesionals to influence decisions on screening and treating people at increased risk of CVD.

Methods

Literature search

A computerized MEDLINE search, 1986 through September 2000, was used to identify studies that measured the tHcy concentration in general population-based samples. The search results with 'homocysteine' as *key-word* were combined with the names of the countries of interest, inserted in the *address of author* field. In addition, reference lists of all identified articles were searched for additional relevant studies.

Study populations

In September 2000, corresponding authors of publications of interest were contacted with a request for data. In total, over 55 letters and e-mails were sent to authors believed to be working in Sweden, Germany, UK, Ireland, France, Spain, Portugal, Italy, Norway, Finland, Denmark, the Netherlands, Belgium and Austria. Owing to changes in either the addresses of corresponding authors, the absence of data on HTEN and/or UNFAVCHOL, diseased populations or unwillingness to provide data, this paper is based on data from nine different study populations from six different European countries (Norway, UK, Germany, the Netherlands, Portugal, France).

Data collection and definition of study variables

On a provided form, the individual study authors could fill out the number of subjects with HHCY, UNFAVCHOL and HTEN, and the number of subjects with a combination of these CVD risk factors.

HHCY was defined as a tHcy concentration $>15\,\mu$mol/l (Ueland *et al*, 1993). As there may be substantial variation in the measured tHcy concentration between laboratories (Eliason *et al*, 1999; Tripodi *et al*, 2001), we adapted this cutoff point for those laboratories for which we had information on the difference in tHcy concentration with the laboratory of the University of Bergen, Norway that set the cutoff point. Thus, HHCY in two Dutch studies (Stehouwer *et al*, 1998; de Bree *et al*, 2001b) was defined as a tHcy concentration $>17.4\,\mu$mol/l. The method used (te Poele Pothoff *et al*, 1995) in these studies showed a systematic difference of $+2.4\,\mu$mol/l compared to the laboratory in Bergen (de Bree *et al*, 2001b).

UNFAVCHOL was defined as a total cholesterol level ≥ 6.5 mmol/l and/or HDL cholesterol level ≤ 0.9 mmol/l and/or the use of cholesterol-lowering medication (European Atherosclerosis Society, 1987). HTEN was defined as a diastolic blood pressure ≥ 95 mmHg and/or a systolic blood pressure ≥ 160 mmHg and/or the use of blood pressure-lowering medication (Working Group on Risk and High Blood Pressure, 1985).

The following exceptions were made for the definitions of UNFAVCHOL and HTEN. Nygard *et al* (1995) defined UNFAVCHOL with data based only on the total cholesterol level and did not have data on blood pressure-lowering medication. Herrmann *et al* (1999) defined UNFAVCHOL as the total cholesterol concentration above 6.21 mmol/l and defined HTEN only with the use of blood pressure-lowering medication. Dierkes and Westphal (2000, personal communication) defined HTEN as systolic blood pressure >140 mmHg and/or the use of antihypertensive drugs.

Of the nine study populations, three analyzed blood for tHcy using nonfasting subjects (Nygard *et al*, 1995; Stehouwer *et al*, 1998; de Bree *et al*, 2001b), whereas in the six remaining studies, fasting subjects were used (Bates *et al*, 1997; Herrmann *et al*, 1999; Hoogeveen *et al*, 2000; Araujo *et al*, 2000; mennen *et al*, 2002)(Dierkes and Westhal, 2000, personal communication). For an optimal tHcy measurement, subjects are recommended to be fasting (Refsum *et al*, 1997). Yet, a recent study contradicts this by showing that the interindividual variation at 0800 hours in the morning after an overnight fast is higher (11%) than the variation in the nonfasting state at 1200 (7.8%) and 1400 (6.8%) hours

(Fokkema *et al*, 2003). Therefore, more research is needed to indicate whether subjects should be fasting or not.

Statistical analyses

For convenience, the data were delivered by the original investigators as the total number of men and women (separately for 10-y age classes) with HHCY, UNFAVCHOL, HTEN and all possible combinations. This means that some subjects appear in more than one column: for example, a subject with a combination of HHCY&UNFAVCHOL does also appear in the column 'total HHCY' and in the column 'total UNFAVCHOL'. In Microsoft® excel 97 SR-2, we calculated the number of subjects with isolated HHCY as follows: [(n_{total} HHCY)−((n_{total} HHCY&UNFAVCHOL−n_{total} HHCY&UNFAVCHOL&HTEN) + (n_{total} HHCY&HTEN−n_{total} HHCY&UNFAVCHOL&HTEN) + n_{total} HHCY&UNFAVCHOL&HTEN)]. The number of subjects with only HHCY&UNFAVCHOL was calculated with (n_{total} HHCY&UNFAVCHOL–n_{total} HHCY&UNFAVCHOL&HTEN) and the number of subjects with only HHCY&HTEN with (n_{total} HHCY&HTEN−n_{total} HHCY&UNFAVCHOL&HTEN). The number of subjects with isolated UNFAVCHOL, HTEN and their isolated combinations was calculated in a similar manner. These calculations were made for three age classes (20–40, 40–60 and 60+ years), for men and women separately and combined.

Note that the contributing authors did not provide individual data of their study populations; only the number of subjects above predefined threshold levels was provided. It was therefore impossible to reanalyze the data with other definitions for HHCY, UNFAVCHOL and HTEN. Moreover, due to the lack of individual data, confidence intervals for our estimates could not be estimated.

If the investigated risk factors occur independently of each other, the expected prevalence of, for example, HHCY&UNFAVCHOL = (observed total prevalence of HHCY × observed total prevalence of UNFAVCHOL). If the risk factors cluster, the prevalence of the combination is higher than the product of the separate total prevalence of the risk factors. To analyze whether the combinations (i) HHCY&UNFAVCHOL, (ii) HHCY&HTEN, (iii) UNFAVCHOL&HTEN, (iv) HHCY&UNFAVCHOL&HTEN occurred more often than expected under the assumption that the risk factors are independent, loglinear models were used. The loglinear model treats all variables as response variables and tests the statistical (in)dependence between them. In these models, the effect of sex, age (20–40, 40–60, 60+ years) and study population were controlled for. These analyses were carried out using the PROC CATMOD procedure of SAS statistical software (version 6.12) (SAS institute Inc., Cary, NC, USA).

Results

The number of men and women per study and age class is given in Table 1. The majority of subjects were between 40 and 60 y. The largest number of data was derived from the Hordaland study in Norway, whereas the smallest number of data came from Portugal. Overall, the number of men and women was equal. Table 2 presents data on the mean levels of the CVD risk factors and the *total* prevalences of HHCY, HTEN and UNFAVCHOL per study, for men and women separately. Differences in mean levels or prevalences were partly due to true differences between countries with risk factor levels generally lower in Southern *vs* Northern European countries. However, they also reflected the different criteria used for selection of the original study population. The

Table 1 Number of men and women in each age class in the nine study populations

		Men				*Women*		
Country, name of study (when given)	*Reference*	N *Total*	*20–40 y (N)*	*40–60 y (N)*	*60+ y (N)*	*20–40 y (N)*	*40–60 y (N)*	*60+ y (N)*
Norway, Hordaland Study	Nygard *et al* (1995)[a]	18 044		6382	2191		6756	2715
UK, National Diet and Nutrition Survey	Bates *et al* (1997)[b]	470			259			211
Germany	Herrmann *et al* (1999)[c]	267	12	1	79	30	4	141
Germany	Dierkes & Westhal (2000)	82		12		20	50	
The Netherlands, Hoorn Study	Hoogeveen *et al* (2000)[d]	631		121	183		76	251
The Netherlands, MORGEN study	De Bree *et al* (2001)[a]	3025	719	718	56	718	718	96
The Netherlands, Zutphen Study	Stehouwer *et al* (1998)	878			878			
Portugal	Araujo *et al* (2000)[e]	101	31	39	1	16	13	1
France, SUVIMAX Study	Mennen *et al* (2002)	1991		691	168	35	991	106
Total		25 489	762	7964	3815	819	8608	3521

Compared to the original publication:
[a]about 2000 extra subjects were included;
[b]only the free living subjects were included;
[c]about 200 subjects were not included;
[d]only the control subjects were included;
[e]only the blood donors were included and about 80 extra blood donors were included.

Table 2 Mean plasma THcy concentration, diastolic and systolic blood pressure, total and HDL cholesterol concentration and *total* prevalences of HHCY, HTEN and UNFAVCHOL in the nine study populations

	Men (n = *12 541*)								*Women* (n = *12 948*)							
Country, Ref (see table legend)	*THcy (μmol/l)*	*HHCY (%)*	*Diabp (mmHg)*	*Sysbp (mmHg)*	*HTEN (%)*	*Totchol (mmol/l)*	*HDL (mmol/l)*	*UNFAVCHOL (%)*	*THcy (μmol/l)*	*HHCY (%)*	*Diabp (mmHg)*	*Sysbp (mmHg)*	*HTEN (%)*	*Totchol (mmol/l)*	*HDL (mmol/l)*	*UNFAV CHOL (%)*
Norway, 1[a]	11.8	11.4	82.8	138.2	20.5	5.9	NA	26.6	10.2	6.9	79.1	131.9	17.1	5.9	NA	28.1
UK, 2[b]	15.7	50.2	NA	NA	53.3	NA	NA	44.4	14.7	34.1	NA	NA	65.9	NA	NA	49.3
Germany, 3[c]	15.1[d]	28.3	NA	NA	4.3	NA	NA	22.8	15.1[d]	32.0	NA	NA	13.1	NA	NA	26.3
Germany, 4	NA	16.7	NA	NA	0	NA	NA	33.3	NA	8.6	NA	NA	11.4	NA	NA	17.1
The Netherlands, 5[e]	11.5[d]	26.6	82[d]	139[d]	34.2	6.7[d]	1.3[d]	54.3	11.5[d]	14.4	82[d]	139[d]	42.5	6.7[d]	1.3[d]	62.7
The Netherlands, 6	14.6	14.4	79.7	124.3	11.0	5.2	1.2	26.7	13.1	8.9	75.8	117.9	10.1	5.2	1.5	15.7
The Netherlands, 7	15.9	25.1	85.5	151.1	42.4	6.1	1.1	26.4	—	—	—	—	—	—	—	—
Portugal, 8[f]	9.0[d]	5.6	NA	NA	5.6	NA	NA	39.4	9.0[d]	3.3	NA	NA	6.7	NA	NA	10.0
France, 9	10.8	12.6	83.8	130.3	13.2	5.9	NA	27.5	8.7	3.9	77.9	121.5	4.2	5.7	NA	21.7
Mean and range	12.4 9.0–15.9		82.7 79.7–85.5	136.9 124.3–151.1		5.8 5.2–6.7	1.2 1.1–1.3		10.6 8.7–15.1		86.5 75.8–79.1	142.4 117.9–139		5.8 5.2–6.7	1.5 1.3–1.5	

1—Nygard *et al* (1995); 2—Bates *et al* (1997); 3—Herrmann *et al* (1999); 4—Dierkes & Westhal (2000); 5—Hoogeveen *et al* (2000); 6—De Bree *et al* (2001a); 7—Stehouwer *et al* (1998); 8—Araujo *et al* (2000); 9—Mennen *et al* (2002).

THcy = total homocysteine concentration; HHCY = hyperhomocysteinemia; Diabp = diastolic blood pressure; Sysbp = systolic blood pressure; HTEN = hypertension; Totchol = total cholesterol concentration; HDL = HDL cholesterol concentration; UNFAVCHOL = unfavorable cholesterol profile; NA = No information available on these mean levels in the original publication (or data on the prevalences only were provided as personal communication).

[a]Compared to the original publication about 2000 extra subjects were included.

[b]Only the values of the free living subjects of this population were included.

[c]Compared to the original publication about 200 subjects were not included.

[d]Mean value of men and women together.

[e]Only the values of the control subjects of this population were included.

[f]Only the values of blood donors were included and compared to the original publication, about 80 extra blood donors were included.

prevalence of risk factors was high in the UK study, but this was an elderly population. Thus, Table 2 should be interpreted in conjunction with Table 1.

The prevalence of total HHCY, HTEN and UNFAVCHOL within each study was higher in men than in women (Table 2), but the relation between age and the prevalence of these CVD risk factors was in general not different for men and women; therefore we combined men and women for the analysis on all European data. Figure 1 shows that with increasing age, the prevalence of isolated HHCY decreased somewhat. This result was caused by a relatively high prevalence of isolated HHCY (9.2%) in Dutch adults aged 20–40 y of the MORGEN study, providing 91% of the data in this age group. The prevalence of isolated UNFAVCHOL and isolated HTEN increased with increasing age, and the same was true for all possible combinations of the risk factors. The high prevalence of UNFAVCHOL&HTEN in the age category 60+ y, was mainly due to a high prevalence (26%) in Norwegian women. Without the data of the Hordaland study, the prevalence of UNFAVCHOL&HTEN was only 10.3%.

The total prevalence of the CVD risk factors in the total European study population can be derived by adding up the data in Figure 1. The total prevalence of HHCY was 10.7% (8.5 + 1.8 + 0.3 + 0.1) in the age category 20–40 y, 7.3% in the age category 40–60 y and 19.2% in the age category 60+ y. The total prevalence of UNFAVCHOL rose with age from 13.2 via 19.2 to 49.3%, and that of HTEN from 3.2 via 10.0 to 42.1%, in the respective age groups. Although the prevalences in some age groups were influenced by the data of the largest study populations, Table 3 shows that the isolated prevalences of HHCY, UNFAVCHOL and HTEN were comparable after exclusion of the data of the Dutch and Norwegian data. The total prevalences increased after exclusion of the larger studies, with a maximum increase of 7.2%.

Figure 2 summarizes the data according to the prevalence of the number (0–3) of CVD risk factors, independent of whether this was HHCY, UNFAVCHOL and/or HTEN. The prevalence of at least one CVD risk factor increased with age. In the 20–40 y age category, 76% of the population had no risk factor, contrasted with only 24.9% in the oldest age category. Nearly no subject in the youngest age category had three risk factors, whereas 4.6% of the older subjects did so.

Table 4 shows the expected and observed values of the various combinations of the three CVD risk factors. To calculate the expected values, the observed total prevalences of HHCY, UNFAVCHOL, HTEN are required (given in the table). After adjustments for age, sex and study center, the combinations HHCY&HTEN and UNFAVCHOL&HTEN occurred more often than was expected on the basis of chance ($P<0.0001$), as did the combination HHCY&UNFAVCHOL&HTEN ($P=0.003$). There was no clustering of HHCY and UNFAVCHOL ($P=0.4$).

Discussion

Our data indicate that one out of every nine subjects (10.9%) in these European populations suffers from HHCY. In half of these cases (5.6%), these subjects also have UNFAVCHOL and/or HTEN. The combinations of HHCY with UNFAVCHOL and/or HTEN all increased with age, confirming that elderly people in particular suffer from more than one CVD risk factor.

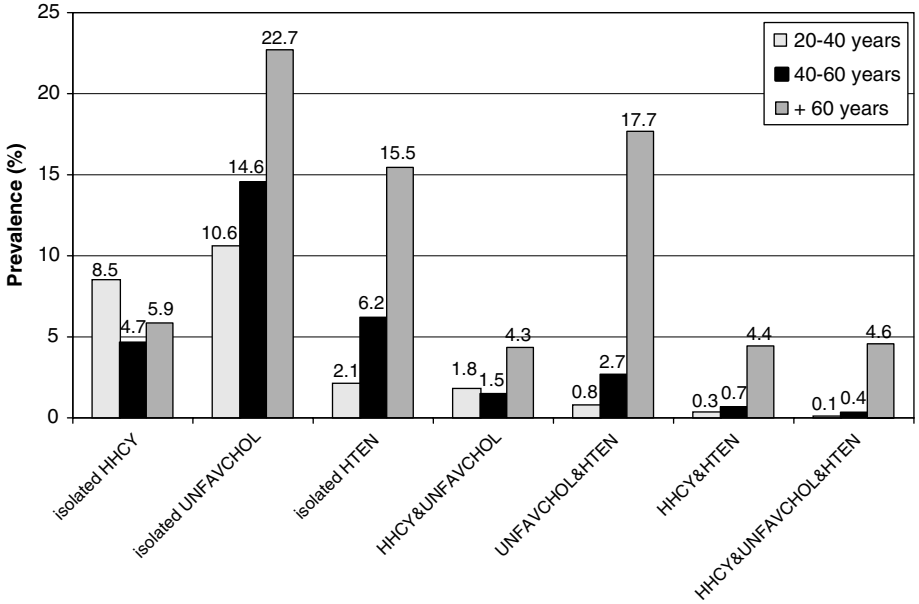

Figure 1 Prevalence of isolated hyperhomocysteinemia (HHCY), isolated unfavorable cholesterol profile (UNFAVCHOL), isolated hypertension (HTEN) and combinations of these risk factors in European men and women, stratified by age.

Table 3 Isolated and total prevalences of HHCY, UNFAVCHOL and HTEN in European men and women (aged 20 + y), with and without the inclusion of the two largest studies

	Isolated prevalences			*Total prevalences*		
	HHCY	*UNFAVCHOL*	*HTEN*	*HHCY*	*UNFAVCHOL*	*HTEN*
All studies ($n=25\,489$)	5.3	16.6	8.6	10.9	27.4	18.8
Without the MORGEN study ($n=22\,464$)	4.9	16.9	9.0	10.8	28.3	19.9
Without the Hordaland study ($n=7445$)	7.4	16.7	8.5	15.4	27.6	19.0
Without both the MORGEN and the Hordaland study ($n=4420$)	7.4	18.2	10.5	18.0	32.0	24.7

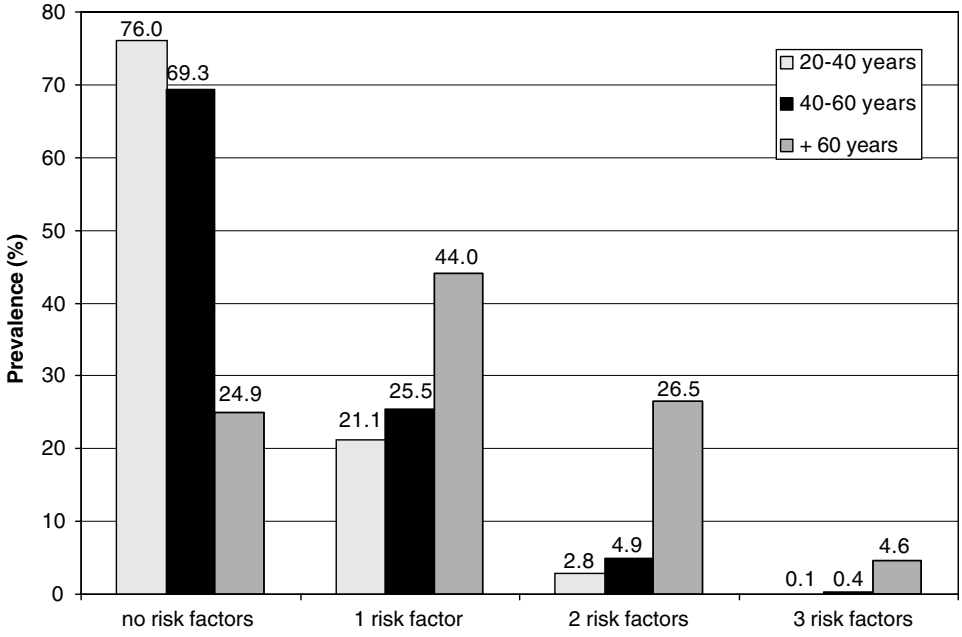

Figure 2 Prevalence of CVD risk factors (HHCY, UNFAVCHOL and/or HTEN) in European men and women, stratified by age. No risk factors = no HHCY, no UNFAVCHOL and no HTEN; 1 risk factor = either HHCY, UNFAVCHOL or HTEN; 2 risk factors = either HHCY&UNFAVCHOL, UNFAVCHOL&HTEN or HHCY&HTEN; 3 risk factors = HHCY&UNFAVCHOL&HTEN.

Table 4 Comparison of expected and observed prevalences of combinations of HHCY, UNFAVCHOL and HTEN

Expected values		*Observed values (see Figure 4)*	
		Total HHCY ($5.3+2.3+1.7+1.5$) = 10.8%	
		Total UNFAVCHOL ($16.7+6.9+2.3+1.5$) = 27.4%	
		Total HTEN ($8.6+6.9+1.7+1.5$) = 18.7%	
Total HHCY&UNFAVCHOL	$100*(0.108\times0.274)=3.0\%$	Total HHCY&UNFAVCHOL	3.9%
Total UNFAVCHOL&HTEN	$100*(0.274\times0.187)=5.1\%$	Total UNFAVCHOL&HTEN	8.4%*
Total HHCY&HTEN	$100*(0.108\times0.187)=2.0\%$	Total HHCY&HTEN	3.2%*
Total HHCY&UNFAVCHOL&HTEN	$100*(0.108\times0.274\times0.187)=0.6\%$	Total HHCY&UNFAVCHOL&HTEN	1.5%*

*The observed prevalence of this combination is statistically significantly ($P<0.004$) higher than the expected values. For these analyses we used loglinear models in which we adjusted for age, sex and study center (see Methods).

To judge these data properly, it is important to first discuss some internal validity aspects. For an optimal tHcy measurement, whole blood should be cooled immediately or should be centrifuged within 1 h after drawing. At room temperature, the blood cells will continue to export homocysteine to plasma (Andersson *et al*, 1992; Malinow *et al*, 1994), leading to artificially higher tHcy concentrations (de Bree *et al*, 2001b). Two studies did not treat whole blood according to this recommendation (Stehouwer *et al*, 1998; Mennen *et al*, 2002). This did not greatly affect our estimates: the prevalence of total HHCY was 10.6% in the studies that centrifuged blood within 1 h *vs* and 12.9% in those that did

not. Furthermore, there is the effect of measurement errors and intraindividual variation. The risk factors in the included studies were only measured once, as is usually done in large-scale studies, this will have led to an overestimation of the number of subjects above the chosen threshold levels. Finally, three studies applied other definitions of UNFAVCHOL and HTEN (Nygard *et al*, 1995; Herrmann *et al*, 1999) (Dierkes and Westhal, 2000, personal communication). This has led to a difference in the estimate for isolated UNFAVCHOL only, which was lower in the 40–60 y old category (13.2 *vs* 19.7% in the studies that did not *vs* did use our definitions), but higher in the oldest age category (25.3 *vs* 16.6%). An underestimation was expected as these studies (Herrmann *et al*, 1999; Nygard *et al*, 1995) did not have data on the HDL-cholesterol level. However, it is known that the cholesterol concentration is, in general, higher in Northern than in Southern European countries (Verschuren *et al*, 1995), and it is particularly high in Norway (Johansson *et al*, 1996).

Secondly, it is important to discuss to what extent these data can be generalized to the 'European population.' Firstly, for this inventory, as many studies as possible were identified that contained relevant data. However, due to reasons described in Methods, the final number of included studies was low (nine out of 55). However, the data of two of the largest surveys in Europe were used, in which the plasma tHcy concentration was measured (Nygard *et al*, 1995; de Bree *et al*, 2001b). More importantly, with or without these data, the isolated prevalences of HHCY, UNFAVCHOL and HTEN did not materially change. Nevertheless, the total prevalences increased. Thus, it seems likely that with the inclusion of the two large surveys, an overestimation of the presence of CVD risk factors has been prevented. On the other hand, the participants of the original studies included in this inventory were volunteers. Generally, individuals who volunteer for these types of studies tend to be healthier than those who do not volunteer, due to a generally more favorable lifestyle profile (Verschuren *et al*, 1993). Using a true random sample of the European population would almost certainly result in higher prevalences of the investigated CVD risk factors. Thus, despite the fact that a single determination of the risk factors will have overestimated our prevalences, it is reasonable to assume that an underestimate rather than overestimate of the actual prevalence of the studied CVD risk factors has taken place.

Standardized protocols and international calibration programs exist (and were applied) for the measurement of cholesterol and blood pressure. A cutoff value of 15 μmol/l was chosen for the tHcy concentration, which is the most widely accepted definition of HHCY in Europe (Ueland *et al*, 1993). Note that the lack of standardization programs applied for the tHcy measurement results in considerable (6 to 15%) interlaboratory variation of the measured tHcy concentration of one sample (Eliason *et al*, 1999; Moller *et al*, 1997, 1999; Pfeiffer *et al*, 1999; Tripodi *et al*, 2001). For most, except two (de Bree *et al*, 2001b; Stehouwer *et al*, 1998) (see Methods) studies, no data were available on how the tHcy measurement in those studies related to the laboratory that set the cutoff value (Ueland *et al*, 1993). Thus, from a practical point of view, it was necessary to ignore the interlaboratory variation and use the cutoff value of 15 μmol/l. The cutoff values used to define UNFAVCHOL and HTEN were, at the time that the subjects were investigated, used by clinicians as a threshold to initiate medical treatment, which makes them the most suitable cutoff values for these data (Working Group on Risk and High Blood Pressure, 1985; European Atherosclerosis Society, 1987). Note, however, that if this study would be performed nowadays, current guidelines would be applied. Nowadays, treatment is based on the total risk profile of a person (including sex, age, total, HDL and LDL cholesterol, blood pressure, diabetes, smoking and family history or premature CVD) and is focused on 'desirable' levels of CVD risk factors rather than cutoff values for increased levels. Using recent guidelines for a desirable tHcy concentration ($<$10–12 μmol/l; Malinow *et al*, 1999; Graham *et al*, 1997; Stanger *et al*, 2003), blood pressure (diastolic blood pressure $<$90 mmHg and systolic blood pressure $<$140 mmHg; Kjeldsen *et al*, 2002) and cholesterol profile (total/HDL ratio$\leq$5; ATP III, 2001) will identify more subjects that may benefit from treatment that lowers their CVD risk factor levels.

There are consistent reports on a weak but statistically significant correlation between tHcy and other CVD risk factors (rarely above 0.2) (Alfthan *et al*, 1994; Brattstrom *et al*, 1994; Arnesen *et al*, 1995; Nygard *et al*, 1995; Malinow *et al*, 1996; de Bree *et al*, 2001a). Despite this large degree of independence on a continuous scale, we showed that the CVD risk factors cluster above defined threshold levels. This can be explained by various mechanisms, for example, HHCY may disturb the endogenous sterol response pathway, leading to increased hepatic biosynthesis and uptake of cholesterol and triglycerides (Werstuck *et al*, 2001). Other explanations include an underlying common lifestyle, a condition provoking HHCY and other components of the CVD risk profile such as renal failure or diabetes, or the fact that some drugs in CVD therapy increase the tHcy concentration (de Lorgeril *et al*, 1999; Dierkes *et al*, 1999; Westphal *et al*, 2001). A large European case–control study showed that the plasma tHcy concentration and conventional risk factors such as smoking and HTEN interact to affect the risk of CVD. This was shown by the fact that the odds ratio for CVD of subjects with HHCY in combination with HTEN was 11.3, whereas based on an additive interaction the expected odds ratio would have been 5.4 (Graham *et al*, 1997).

This inventory showed that 10.7% of the Europeans studied aged 20–40 y, 7.3% aged 40–60 y and 19.2% aged 60+ y have HHCY either isolated or in combination with UNFAVCHOL and/or HTEN. In addition, 76% of the elderly have more than one of the investigated CVD risk factors, whereas 75% of the younger adults have none. This is important information for healthcare professionals who may, based on these results, decide to routinely screen the

elderly for HTEN, UNFAVCHOL and HHCY. Targeted treatment of the risk factors present may consequently minimize the risk of CVD. The same approach is probably less cost-effective in younger subjects, and screening may only be adopted if there are additional indications, such as family history of CVD or an underlying disease.

The treatment chosen depends on the type of risk factor and the degree to which it is increased. Under well-controlled conditions, dietary interventions have been succesful in treating HHCY (Brouwer *et al*, 1999; Riddell *et al*, 2000; Ashfield-Watt *et al*, 2003), UNFAVCHOL (Hu *et al*, 2001) and HTEN (Appel *et al*, 1997). However, some of the intervention diets required extreme adaptations in the dietary habits of the subjects (eg consuming >5 servings of fruit/day; Appel *et al*, 1997) and may not be suitable in a 'free-living' situation. This is why extremely elevated total cholesterol levels and blood pressure are mostly treated with medications (like statins/fibrates and diuretics/beta-blockers, etc), but these are expensive and may have unwanted side-effects. On the other hand, even extremenly high tHcy concentrations can be lowered with the safe, inexpensive and effective therapy of folic acid supplementation or the consumption of fortified foods.

Following the guidelines of the American Heart Association, several European countries (Germany, Austria, Switserland and the Netherlands) have adopted guidelines to screen for HHCY in subjects with a risk profile predisposing to a higher CVD risk (Netherlands Heart Foundation, 2001; Stanger *et al*, 2003), like those with UNFAVCHOL, HYPTEN and smokers. In case of HHCY, a daily dose of $\sim$500 (200–800) μg of folic acid (possibly in combination with vitamin B_6 and B_{12}) may be prescribed alongside a traditional treatment of their other risk factors (Netherlands Heart Foundation, 2001; Stanger *et al*, 2003). Such a dose would on average lower the tHcy concentration with 25% ($\sim 3\,\mu$mol/l) (Clarke and Armitage, 2000; van Oort *et al*, 2003), which in turn may lower their risk of ischemic heart disease with 11% and of stroke with 19% (The Homocysteine Studies Collaboration, 2002).

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